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REMARKS/ARGUMENTS

Claims 53-63 and 65-77 have been resubmitted. Claims 53 and 66 have been amended. No claims have been canceled and no new claims have been added.

35 U.S.C. §103

The Examiner has maintained the rejection of claims 53-63 and 65-77 under 35 U.S.C. §103(a) as being unpatentable over the Mizuno patent in view of the Sah application, the Anseth reference, the Cooke patent and the Spiro patent. Applicants respectfully traverse and request reconsideration.

The Mizuno patent discloses methods for producing a multi-layered biological construct having an integration layer and a cellular support matrix layer. It may also optionally have a protection layer over the cellular support matrix layer. The integration layer is applied to the tissue and then the cell support is added to the integration layer, where it is adhered to the tissue through the integration layer. The cellular support matrix is a three-dimensional matrix in which cells are incubated to form a "neo-tissue" before being adhered to the tissue. The Mizuno patent disclose that it is prepared by introducing the matrix into a solution of living cells such that the solution enters the sponge-like matrix by capillary action (column 2, line 65 to column 3, line 3; and column 3, lines 42 to 51). The Mizuno patent also states that "the cellular support matrix of the present invention acts like a sponge that wicks up (and evenly distributes throughout the intertices of the matrix) cells suspended in a sol-gel solution..." (column 11, lines 49 to 52). Moreover, the cell-infused matrix is then incubated to form a "neo-tissue" which is defined as a cellular composition that approximates the form and function of the tissue *in situ* (column 5, lines 54 to

56). Alternatively, cells may be grown into a three dimensional "neo-tissue" form without the use of the matrix before being used *in vivo*.

In contrast, the claimed method of the present invention provides a first polymerizable mixture having a first polymerizable material and first cells, where the mixture is directly placed in an osteochondral tissue space without being placed in a matrix or cultured before placement. It is then crosslinked to partially get the mixture. The claimed method also provides a second polymerizable mixture having a second polymerizable material, the mixture directly placed with the partially gelled first layer and crosslinking it to partially gel the second mixture. It is contemplated that the first and second mixtures can be injected into the tissue space. See paragraph [0023]. In contrast, the cellular support matrix or neo-tissue of the Mizuno patent are solid and cannot be injected.

In an effort to expedite prosecution of this case, but in no way conceding to the validity of the rejection, Applicants have amended independent claims 53 and 66 to state that the polymerizable mixtures (i.e. first, second or third) are directly placed in an osteochondral tissue space without being placed in a matrix or subsequently cultured. Basis for the amendment may be found in the specification, particularly in paragraph [00128].

The Examiner has noted that the Mizuno patent repeatedly states that the reference method is not limited to specifically disclosed embodiments and that the multilayered design may be fabricated into a variety of forms. It is true that the Mizuno patent made such broad, unsubstantiated, and non-specific statements, but these statements cannot reasonably be interpreted to be that the method disclosed in the Mizuno patent can be modified in any and all possible ways. Otherwise, the Mizuno patent would render any and all other methods for making multilayer tissue constructs obvious. Particularly, Applicants note that the Mizuno patent states that the referenced method covers "all modifications that are within the spirit and scope of the invention..." (Column 25, lines 26 to 30; emphasis added). Therefore, when compared with the present invention, the method of the Mizuno patent, particularly the so-called modification thereof, needs to be considered in light of the Examples and embodiments specifically described in the specification of Mizuno patent, but not to be extrapolated to an unjustifiable proportion. Moreover, the MPEP states that ascertaining the differences between the claimed invention and the prior art requires considering both the invention and the prior art as a whole. MPEP § 2141 II(B). Therefore, the method of the Mizuno patent must be limited to the use of a three-dimension cellular support matrix and/or neo-tissue.

Furthermore, the secondary references fail to cure the deficiencies of Mizuno et al in view of the amended claims.

The Sah application discloses a multi-layered construct having chondrocytes of different phenotypes in each layer. However, in contrast to the present invention, the multi-layered construct of the Sah application is formed *ex vivo*, cultured to form an engineered cartilage construct, and then implanted into the tissue site. Unlike the present invention, there is no exogenous polymerizable material used to form a hydrogel, only the cell-associated matrix formed when the cells are cultured. Paragraphs [0061]-[0067]. As the Sah application teaches, "... the chondrocytes with their cell associated matrix, isolated as described above, are cultured in layers on a semipermeable membrane. Alternatively, one or more of the cell layers that lack a cell-associated matrix can be added to the culture to produce the cohesive cartilage tissue." Paragraph [0064]. In contrast, in the claimed method of the present invention, the multilayered tissue construct in formed *in vivo* and comprises a polymerizable material wherein each layer of the construct is formed by crosslinking the polymerizable material to form a gel material.

The Anseth reference teaches a method of preparing a mono-layer hydrogel *in situ* via photopolymerization. The hydrogel of Anseth reference, however, is cultured *in vitro* and no *in vivo* methods are disclosed. See Figure 7. Moreover, the Anseth reference does not suggest or contemplate a multi-layered hydrogel structure fabricated by partial gelling of each layers followed by further gelling for integration as claimed by the present invention.

The Cook patent discloses a construct in which a biodegradable hydrophilic layer is placed on a biodegradable hydrophobic layer so that biological factors can be attached to the hydrophilic layer. See column 12, lines 11-25 and the Figures. The Cook patent does not disclose the integration of cells or bioactive materials into any of the layers, but instead, discloses attaching biological factors to the surface of the hydrophilic layer.

The Spiro patent discloses a method for making a two-layer construct where each of the layers is formed independently of the other *in vitro*. One layer is then adhered to the other by chemical or mechanical means, again *in vitro*. In contrast, the claimed method of the present invention forms the multi-layered construct *in vivo*. In the present claimed method, a first mixture is applied and partially gelled before a second mixture is added, and also partially gelled before both layers are fully crosslinked to form the construct.

Applicants thus submit that the Mizuno, Cook or Spiro patents, the Sah application nor the Anseth reference, either alone or together, teach the claimed method of the present application. Specifically, none of the references teach or disclose a multi-layered tissue construct formed *in vivo* where a first mixture is added to a tissue space and partially gelled followed by the a second mixture placed on the partially gelled first mixture, where the second mixture is partially gelled. Nor is there any motivation for the skilled artisan to take the *in vitro* methods of the references and modify them to use *in vivo*. Moreover, there is no suggestion or teaching to replace the cellular support matrix or neo-tissue of the Mizuno patent with a non-cultured hydrogel layer to provide the claimed method of the present invention. Applicants therefore respectfully request withdrawal of the rejection.

CONCLUSION

Applicants submit that the amended claims are now in condition for allowance and such allowance is courteously solicited.

In the event the examiner wishes to discuss any aspect of this response, please contact the attorney at the telephone number identified below.

☒ The Commissioner is hereby authorized to charge payment of the following fees with this communication or credit any overpayment to Deposit Account No. 02-3223:

☒ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.

Respectfully submitted,

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